HUMULIN R U-500 - insulin human injection, solution
Eli Lilly and Company

DESCRIPTION

Humulin is synthesized in a special non–disease–producing laboratory strain of *Escherichia coli* bacteria that has been genetically altered by the addition of the gene for human insulin production. Humulin R (U–500) consists of zinc–insulin crystals dissolved in a clear fluid. Humulin R (U–500) is a sterile solution and is for subcutaneous injection. It should not be used intravenously or intramuscularly. The concentration of Humulin R (U–500) is 500 units/mL.
Each milliliter contains 500 units of biosynthetic human insulin, 16 mg glycerin, 2.5 mg Metacresol as a preservative, and zinc–oxide calculated to supplement endogenous zinc to obtain a total zinc content of 0.017 mg/100 units. Sodium hydroxide and/or hydrochloric acid may be added during manufacture to adjust the pH.

CLINICAL PHARMACOLOGY

Adequate insulin dosage permits the diabetic patient to utilize carbohydrates and fats in a comparatively satisfactory manner. Regardless of concentration, the action of insulin is basically the same: to enable carbohydrate metabolism to occur and thus to prevent the production of ketone bodies by the liver. Although, under usual circumstances, diabetes can be controlled with doses in the vicinity of 40 to 60 units or less, an occasional patient develops such resistance or becomes so unresponsive to the effect of insulin that daily doses of several hundred, or even several thousand, units are required. Patients who require doses in excess of 300 to 500 units daily usually have impaired insulin receptor function.
Occasionally, a cause of the insulin resistance can be found (such as hemochromatosis, cirrhosis of the liver, some complicating disease of the endocrine glands other than the pancreas, allergy, or infection), but in other cases, no cause of the high insulin requirement can be determined.
Humulin R (U–500) is unmodified by any agent that might prolong its action; however, clinical experience has shown that it frequently has a time action similar to a repository insulin preparation. It takes effect rapidly but has a relatively long duration of activity following a single dose (up to 24 hours) as compared with other Regular insulins. This effect has been credited to the high concentration of the preparation. The time course of action of any insulin may vary considerably in different individuals or at different times in the same individual. As with all insulin preparations, the duration of action of Humulin R (U–500) is dependent on dose, site of injection, blood supply, temperature, and physical activity.

INDICATIONS AND USAGE

Humulin R (U–500) is especially useful for the treatment of diabetic patients with marked insulin resistance (daily requirements more than 200 units), since a large dose may be administered subcutaneously in a reasonable volume.

CONTRAINDICATIONS

Humulin R (U–500) is contraindicated in hypoglycemia.

WARNINGS

THIS LILLY HUMAN INSULIN PRODUCT DIFFERS FROM ANIMAL–SOURCE INSULINS BECAUSE IT IS STRUCTURALLY IDENTICAL TO THE INSULIN PRODUCED BY YOUR BODY'S PANCREAS AND BECAUSE OF ITS UNIQUE MANUFACTURING PROCESS.
ANY CHANGE OF INSULIN SHOULD BE MADE CAUTIOUSLY AND ONLY UNDER MEDICAL SUPERVISION.

CHANGES IN PURITY, STRENGTH, BRAND (MANUFACTURER), TYPE (REGULAR, NPH, LENTE®, ETC), SPECIES (BEEF, PORK, BEEF–PORK, HUMAN), AND/OR METHOD OF MANUFACTURE (rDNA VERSUS ANIMAL–SOURCE INSULIN) MAY RESULT IN THE NEED FOR A CHANGE IN DOSAGE.

SOME PATIENTS TAKING HUMULIN® (HUMAN INSULIN, rDNA ORIGIN, LILLY) MAY REQUIRE A CHANGE IN DOSAGE FROM THAT USED WITH ANIMAL–SOURCE INSULINS. IF AN ADJUSTMENT IS NEEDED, IT MAY OCCUR WITH THE FIRST DOSE OR DURING THE FIRST SEVERAL WEEKS OR MONTHS.
This insulin preparation contains 500 units of insulin in each milliliter. Extreme caution must be observed in the measurement of dosage because inadvertent overdose may result in irreversible insulin shock. Serious consequences may result if it is used other than under constant medical supervision.

PRECAUTIONS

General

Every patient exhibiting insulin resistance who requires Humulin R (U–500) for control of diabetes should be under close observation until appropriate dosage is established. The response will vary among patients. Some patients can be controlled with a single dose daily; others may require 2 or 3 injections per day. Most patients will show a "tolerance" to insulin, so that minor variations in dosage can occur without the development of untoward symptoms of insulin shock.

Insulin resistance is frequently self–limited; after several weeks or months during which high dosage is required, responsiveness to the pharmacologic effect of insulin may be regained and dosage can be reduced.

Information for Patients
Patients should be instructed regarding their dosage and should be reminded that this formulation requires the administration of a smaller volume of solution than is the case with less concentrated formulations.

Laboratory Tests
Blood and urine glucose, glycohemoglobin, and urine ketones should be monitored frequently.

Drug Interactions
The concurrent use of oral hypoglycemic agents with Humulin R (U–500) is not recommended since there are no data to support such use.
Insulin requirements may be increased by medications with hyperglycemic activity such as corticosteroids, isoniazid, certain lipid-lowering drugs (e.g., niacin), estrogens, oral contraceptives, phenothiazines, and thyroid replacement therapy (*see* CLINICAL PHARMACOLOGY).
Insulin requirements may be decreased in the presence of drugs that increase insulin sensitivity or have hypoglycemic activity, such as oral antidiabetic agents, salicylates, sulfa antibiotics, certain antidepressants (monoamine oxidase inhibitors), angiotensin-converting-enzyme inhibitors, angiotensin II receptor blocking agents, beta-adrenergic blockers, inhibitors of pancreatic function (e.g., octreotide), and alcohol. Beta-adrenergic blockers may mask the symptoms of hypoglycemia in some patients.

Pregnancy
Teratogenic Effects — No reproduction studies have been conducted in animals, and there are no adequate and well–controlled studies in pregnant women. It would be anticipated that the benefits of this insulin preparation would outweigh any risk to the developing fetus.

Nonteratogenic Effects — Insulin does not cross the placenta as does glucose.

Labor and Delivery
Careful monitoring of the patient is required, since the insulin requirement may decrease following delivery.

Nursing Mothers
It is not known whether insulin is excreted in significant amounts in human milk. Because many drugs are excreted in human milk, caution should be exercised when Humulin R (U–500) insulin injection is administered to a nursing woman.

Pediatric Use
There are no special precautions relating to the use of this insulin formulation in the pediatric age group.

ADVERSE REACTIONS
As with other human insulin preparations, hypoglycemic reactions may be associated with the administration of Humulin R (U–500). However, deep secondary hypoglycemic reactions may develop 18 to 24 hours after the original injection of Humulin R (U–500). Consequently, patients should be carefully observed, and prompt treatment of such reactions should be initiated with glucagon injections and/or with glucose by intravenous injection or gavage.
Hypoglycemia
Hypoglycemia is one of the most frequent adverse events experienced by insulin users.
Symptoms of mild to moderate hypoglycemia may occur suddenly and can include:

- sweating
- dizziness
- palpitation
- tremor
- drowsiness
- sleep disturbances
- anxiety
- blurred vision

- hunger
- restlessness
- tingling in the hands, feet, lips, or tongue
- lightheadedness
- inability to concentrate
- headache
- slurred speech
- depressive mood
- irritability
- abnormal behavior
- unsteady movement
- personality changes

Signs of severe hypoglycemia can include:

- disorientation
- unconsciousness
- seizures
- death

Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, medications such as beta–blockers, change in insulin preparations, or intensified control (3 or more insulin injections per day) of diabetes.

A few patients who have experienced hypoglycemic reactions after transfer from animal–source insulin to human insulin have reported that the early warning symptoms of hypoglycemia were less pronounced or different from those experienced with their previous insulin.

Without recognition of early warning symptoms, the patient may not be able to take steps to avoid more serious hypoglycemia. Patients who experience hypoglycemia without early warning symptoms should monitor their blood glucose frequently, especially prior to activities such as driving. Mild to moderate hypoglycemia may be treated by eating foods or taking drinks that contain sugar. Patients should always carry a quick source of sugar, such as candy mints or glucose tablets.

Hypoglycemia when using Humulin R (U–500) can be prolonged and severe.

Lipodystrophy

Rarely, administration of insulin subcutaneously can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue).

Allergy to Insulin

Local Allergy — Patients occasionally experience erythema, local edema, and pruritus at the site of injection of insulin. This condition usually is self–limiting. In some instances, this condition may be related to factors other than insulin, such as irritants in the skin cleansing agent or poor injection technique.

Systemic Allergy — Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalized allergy (anaphylaxis) may be life threatening.

DOSAGE AND ADMINISTRATION

Humulin R (U–500) should only be administered subcutaneously. It is inadvisable to inject Humulin R (U–500) intravenously because of possible inadvertent overdosage.

It is recommended that an insulin syringe or tuberculin–type syringe be used for the measurement of dosage. Variations in dosage are frequently possible in the insulin–resistant patient, since the individual is unresponsive to the pharmacologic effect of the insulin. Nevertheless, accuracy of measurement is to be encouraged because of the potential danger of the preparation.

STORAGE

Insulin should be kept in a cold place, preferably in a refrigerator, but must not be frozen.
Do not inject insulin that is not water–clear. Discoloration, turbidity, or unusual viscosity indicates deterioration or contamination.
Use of a package of insulin should not be started after the expiration date stamped on it.

HOW SUPPLIED

Vials, 500 units/mL, 20 mL (HI–500) (1s), NDC 0002–8501–01
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Eli Lilly and Company, Indianapolis, IN 46285, USA
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PA 3053 AMP

INFORMATION FOR THE PATIENT

HUMULIN® R
REGULAR
U–500 (CONCENTRATED)
INSULIN HUMAN INJECTION, USP
(RDNA ORIGIN)

WARNINGS

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This insulin preparation contains 500 units of insulin in each milliliter. Extreme caution must be observed in the measurement of dosage because inadvertent overdose may result in irreversible insulin shock. Serious consequences may result if it is used other than under constant medical supervision.

DIABETES

Insulin is a hormone produced by the pancreas, a large gland that lies near the stomach. This hormone is necessary for the body's correct use of food, especially sugar. Diabetes occurs when the pancreas does not make enough insulin to meet your body's needs. To control your diabetes, your doctor has prescribed injections of insulin products to keep your blood glucose at a near–normal level. You have been instructed to test your blood and/or your urine regularly for glucose. Studies have shown that some chronic complications of diabetes such as eye disease, kidney disease, and nerve disease can be significantly reduced if the blood sugar is maintained as close to normal as possible. The American Diabetes Association recommends that if your pre-meal glucose levels are consistently above 130 mg/dL or your hemoglobin A_{1c} (HbA_{1c}) is more than 7%, consult your doctor. A change in your diabetes therapy may be needed. If your blood tests consistently show below–normal glucose levels you should also let your doctor know. Proper control of your diabetes requires close and constant cooperation with your doctor. Despite diabetes, you can lead an active and healthy life if you eat a balanced diet, exercise regularly, and take your insulin injections as prescribed.
Always keep an extra supply of insulin as well as a spare syringe and needle on hand. Always wear diabetic identification so that appropriate treatment can be given if complications occur away from home.

REGULAR HUMAN INSULIN

Description

Humulin is synthesized in a special non–disease–producing laboratory strain of *Escherichia coli* bacteria that has been genetically altered by the addition of the gene for human insulin production. Humulin R (U–500) consists of zinc–insulin crystals dissolved in a clear fluid. Humulin R (U–500) has had nothing added to change the speed or length of its action. It takes effect rapidly but has a relatively long duration of activity (up to 24 hours) as compared with other Regular insulins. The time course of action of any insulin may vary considerably in different individuals or at different times in the same individual. As with all insulin preparations, the duration of action of Humulin R (U–500) is dependent on dose, site of injection, blood supply, temperature, and physical activity. Humulin R (U–500), is a sterile solution and is for subcutaneous injection only. It should not be used intravenously or intramuscularly. The concentration of Humulin R (U–500) is 500 units/mL.

Identification
Human insulin by Eli Lilly and Company has the trademark Humulin and is available in 6 formulations — Regular (**R**), NPH (**N**), Lente (**L**), Ultralente® (**U**), 50% Human Insulin Isophane Suspension [NPH]/50% Human Insulin Injection [regular] (**50/50**), and 70% Human Insulin Isophane Suspension [NPH]/30% Human Insulin Injection [regular] (**70/30**). Humulin R (U–500) is the only human insulin by Eli Lilly and Company that has a concentration of 500 units/mL. Your doctor has prescribed the type of insulin that he/she believes is best for you. **DO NOT USE ANY OTHER INSULIN EXCEPT ON HIS/HER ADVICE AND DIRECTION.** Always check the carton and the bottle label for the name and letter designation of the insulin you receive from your pharmacy to make sure it is the same as that your doctor has prescribed.
Always examine the appearance of your bottle of insulin before withdrawing each dose. Humulin R (U–500) is a clear and colorless liquid with a water–like appearance and consistency. Do not use if it appears cloudy, thickened, or slightly colored or if solid particles are visible. Always check the appearance of your bottle of insulin before using, and if you note anything unusual in the appearance of your insulin or notice your insulin requirements changing markedly, consult your doctor.
Storage
Insulin should be stored in a refrigerator but not in the freezer. If refrigeration is not possible, the bottle of insulin that you are currently using can be kept unrefrigerated as long as it is kept as cool as possible (below 30°C [86°F]) and away from heat and light. Do not use insulin if it has been frozen. Do not use a bottle of Humulin R (U-500) after the expiration date stamped on the label.
INJECTION PROCEDURES
Correct Syringe Type
Doses of insulin are measured in **units**. U–500 insulin contains 500 units/mL (1 mL=1 cc). With Humulin R (U–500), it is important to use a tuberculin (or similar) syringe as instructed by your doctor. Failure to use the proper syringe type can lead to a mistake in dosage, causing serious problems for you, such as a blood glucose level that is too low or too high.
Syringe Use
To help avoid contamination and possible infection, follow these instructions exactly.
Disposable plastic syringes and needles should be used only once and then discarded in a responsible manner. **NEEDLES AND SYRINGES MUST NOT BE SHARED.**
Reusable glass syringes and needles must be sterilized before each injection. **Follow the package directions supplied with your syringe.** Described below are 2 methods of sterilizing.
Boiling
1. Put syringe, plunger, and needle in strainer, place in saucepan, and cover with water. Boil for 5 minutes.

2. Remove articles from water. When they have cooled, insert plunger into barrel, and fasten needle to syringe with a slight twist.

3. Push plunger in and out several times until water is completely removed.

Isopropyl Alcohol
If the syringe, plunger, and needle cannot be boiled, as when you are traveling, they may be sterilized by immersion for at least 5 minutes in Isopropyl Alcohol, 91%. Do not use bathing, rubbing, or medicated alcohol for this sterilization. If the syringe is sterilized with alcohol, it must be absolutely dry before use.
Preparing the Dose
1. Wash your hands.

2. Inspect the insulin. Humulin R (U–500) should look clear and colorless. Do not use Humulin R (U–500) if it appears cloudy, thickened, or slightly colored or if solid particles are visible.

3. If using a new bottle, flip off the plastic protective cap, but **do not** remove the stopper. When using a new bottle, wipe the top of the bottle with an alcohol swab.

4. Draw air into the syringe equal to your insulin dose. Put the needle through the rubber top of the insulin bottle and inject the air into the bottle.

5. Turn the bottle and syringe upside down. Hold the bottle and syringe firmly in one hand.

6. Making sure the tip of the needle is in the insulin, withdraw the correct dose of insulin into the syringe.

7. Before removing the needle from the bottle, check your syringe for air bubbles which reduce the amount of insulin in it. If bubbles are present, hold the syringe straight up and tap its side until the bubbles float to the top. Push them out with the plunger and withdraw the correct dose.

8. Remove the needle from the bottle and lay the syringe down so that the needle does not touch anything.

Injection

Once you have chosen an injection site, cleanse the skin with alcohol where the injection is to be made. Stabilize the skin by spreading it or pinching up a large area. Insert the needle as instructed by your doctor. Push the plunger in as far as it will go. Pull the needle out and apply gentle pressure over the injection site for several seconds. **Do not rub the area.** To avoid tissue damage, give the next injection at a site at least 1/2 inch from the previous site.

DOSAGE

Your doctor has told you which insulin to use, how much, and when and how often to inject it. Because each patient's case of diabetes is different, this schedule has been individualized for you.

Your usual insulin dose may be affected by changes in your food, activity, or work schedule. Carefully follow your doctor's instructions to allow for these changes. Other things that may affect your insulin dose are:

Illness

Illness, especially with nausea and vomiting, may cause your insulin requirements to change. Even if you are not eating, you will still require insulin. You and your doctor should establish a sick day plan for you to use in case of illness. When you are sick, test your blood glucose/urine glucose and ketones frequently and call your doctor as instructed.

Pregnancy

Good control of diabetes is especially important for you and your unborn baby. Pregnancy may make managing your diabetes more difficult. If you are planning to have a baby, are pregnant, or are nursing a baby, consult your doctor.

Medication

Insulin requirements may be increased if you are taking other drugs with blood–glucose–raising activity, such as oral contraceptives, corticosteroids, or thyroid replacement therapy. Insulin requirements may be reduced in the presence of drugs that lower blood glucose or affect how your body responds to insulin, such as oral antidiabetic agents, salicylates (for example, aspirin), sulfa antibiotics, alcohol, certain antidepressants and some kidney and blood pressure medicines. Your Health Care Professional may be aware of other medications that may affect your diabetes control. Therefore, always discuss any medications you are taking with your doctor.

Exercise

Exercise may lower your body's need for insulin during and for some time after the activity. Exercise may also speed up the effect of an insulin dose, especially if the exercise involves the area of injection site (for example, the leg should not be used for injection just prior to running). Discuss with your doctor how you should adjust your regimen to accommodate exercise.

Travel

Persons traveling across more than 2 time zones should consult their doctor concerning adjustments in their insulin schedule.

COMMON PROBLEMS OF DIABETES

Hypoglycemia (Low Blood Sugar)

Hypoglycemia (too little glucose in the blood) is one of the most frequent adverse events experienced by insulin users. It can be brought about by:

1. **Missing or delaying meals.**
2. Taking too much insulin.
3. Exercising or working more than usual.
4. An infection or illness (especially with diarrhea or vomiting).
5. A change in the body's need for insulin.
6. Diseases of the adrenal, pituitary, or thyroid gland, or progression of kidney or liver disease.
7. Interactions with certain drugs, such as oral antidiabetic agents, salicylates (for example, aspirin), sulfa antibiotics, certain antidepressants and some kidney and blood pressure medicines.
8. Consumption of alcoholic beverages.

Symptoms of mild to moderate hypoglycemia may occur suddenly and can include:

- sweating
- drowsiness
- dizziness
- sleep disturbances
- palpitation
- anxiety

- tremor
- hunger
- restlessness
- tingling in the hands, feet, lips, or tongue
- lightheadedness
- inability to concentrate
- headache
- blurred vision
- slurred speech
- depressive mood
- irritability
- abnormal behavior
- unsteady movement
- personality changes

Signs of severe hypoglycemia can include:

- disorientation
- unconsciousness
- seizures
- death

Therefore, it is important that assistance be obtained immediately.

Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, medications such as beta–blockers, change in insulin preparations, or intensified control (3 or more insulin injections per day) of diabetes.

A few patients who have experienced hypoglycemic reactions after transfer from animal–source insulin to human insulin have reported that the early warning symptoms of hypoglycemia were less pronounced or different from those experienced with their previous insulin.

Without recognition of early warning symptoms, you may not be able to take steps to avoid more serious hypoglycemia. Be alert for all of the various types of symptoms that may indicate hypoglycemia. Patients who experience hypoglycemia without early warning symptoms should monitor their blood glucose frequently, especially prior to activities such as driving. If the blood glucose is below your normal fasting glucose, you should consider eating or drinking sugar–containing foods to treat your hypoglycemia.

Mild to moderate hypoglycemia may be treated by eating foods or taking drinks that contain sugar. Patients should always carry a quick source of sugar, such as candy mints or glucose tablets. More severe hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally or who are unconscious require an injection of glucagon or should be treated with intravenous administration of glucose at a medical facility.

Hypoglycemia when using Humulin R (U–500) can be prolonged and severe. All hypoglycemic episodes should be reported to your doctor.

You should learn to recognize your own symptoms of hypoglycemia. If you are uncertain about these symptoms, you should monitor your blood glucose frequently to help you learn to recognize the symptoms that you experience with hypoglycemia.

If you have frequent episodes of hypoglycemia or experience difficulty in recognizing the symptoms, you should consult your doctor to discuss possible changes in therapy, meal plans, and/or exercise programs to help you avoid hypoglycemia.

Hyperglycemia and Diabetic Ketoacidosis (DKA)

Hyperglycemia (too much glucose in the blood) may develop if your body has too little insulin. Hyperglycemia can be brought about by:

1. Omitting your insulin or taking less than the doctor has prescribed.

2. Eating significantly more than your meal plan suggests.

3. Developing a fever, infection, or other significant stressful situation.

In patients with type 1 or insulin–dependent diabetes, prolonged hyperglycemia can result in DKA. The first symptoms of DKA usually come on gradually, over a period of hours or days, and include a drowsy feeling, flushed face, thirst, loss of appetite, and fruity odor on the breath. With DKA, urine tests show large amounts of glucose and ketones. Heavy breathing and a rapid pulse are more severe symptoms. If uncorrected, prolonged hyperglycemia or DKA can lead to nausea, vomiting, dehydration, loss of consciousness or death. Therefore, it is important that you obtain medical assistance immediately.

Lipodystrophy

Rarely, administration of insulin subcutaneously can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue). If you notice either of these conditions, consult your doctor. A change in your injection technique may help alleviate the problem.

Allergy to Insulin

Local Allergy — Patients occasionally experience redness, swelling, and itching at the site of injection of insulin. This condition, called local allergy, usually clears up in a few days to a few weeks. In some instances, this condition may be related to factors other than insulin, such as irritants in the skin cleansing agent or poor injection technique. If you have local reactions, contact your doctor.

Systemic Allergy — Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalized allergy may be life threatening. If you think you are having a generalized allergic reaction to insulin, notify a doctor immediately.

ADDITIONAL INFORMATION

Additional information about diabetes may be obtained from your diabetes educator.

DIABETES FORECAST is a magazine designed especially for people with diabetes and their families. It is available by subscription from the American Diabetes Association (ADA), P.O. Box 363, Mt. Morris, IL 61054-0363, 1-800-DIABETES (1-800-342-2383).

Another publication, **COUNTDOWN**, is available from the Juvenile Diabetes Research Foundation International (JDRFI), 120 Wall Street 19th Floor, New York, NY 10005, 1-800-533-CURE (1–800–533–2873).

Additional information about Humulin can be obtained by calling The Lilly Answers Center at 1-800-LillyRx (1-800-545-5979).

Patient Information revised September 10, 2007

Eli Lilly and Company, Indianapolis, IN 46285, USA

PA 3053 AMP

PACKAGE CARTON – HUMULIN R U-500 Vial 20 mL 1ct

Lilly

NDC 0002-8501-01

20 mL

HI-500

(Concentrated)

U-500

Humulin® R

REGULAR

insulin human injection, USP

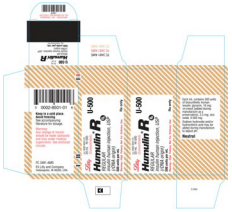
(rDNA origin)

Rx

500 units per mL

Warning—High Potency Not For Ordinary Use

Rx only



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